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Letter to the Editor

Impact of pericardial injury on inflammatory biomarkers early post myocardial infarction
A cardiovascular magnetic resonance (CMR) study

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Acute myocardial infarction (MI) is typically followed by a systematic inflammatory response with release of plasma acute phase proteins such as C-reactive protein (CRP) [1]. Studies in animal models have shown deposition of CRP and complement in the infarct and border areas, suggesting that CRP may accentuate local post-infarction inflammatory response, and promote tissue injury and infarct expansion [2]. However, the injury caused by abrupt coronary occlusion is not necessarily confined to the myocardium but may affect the pericardium as well [3]. Using comprehensive cardiovascular magnetic resonance (CMR) imaging we sought to study the relationship between CRP levels and cardiac injury in 190 consecutive, successfully reperfused ST-segment elevation MI patients (mean age 59 ± 11 years, 84% male). Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. CMR studies were performed 2–5 days post-infarction. Cine CMR was used to quantify LV volumes and function. T2-weighted imaging and late gadolinium enhancement imaging were used to characterize and to quantify the jeopardized myocardium. Pericardial injury was defined as presence of pericardial fluid >4 mm and/or enhancement of the pericardial layers. As CRP at 48 h post-reperfusion corresponded to the maximum CRP value (median 2 days, IQR, 1–3), the value at day 2 was used to explore correlations with other clinical, biochemical and CMR parameters. Nine patients were excluded from analysis (insufficient CMR image quality n = 1, insufficient CRP data n = 2, non-cardiac related causes of CRP increase n = 6) yielding a total of 181 patients. The culprit coronary artery was the left anterior descending, right coronary, and circumflex coronary in 83, 76 and 22 patients respectively. Peak troponin I was 66 μg/l (median, IQR, 28–123) and peak CRP at day 2 was 24 mg/dl (median, IQR, 9–52). LV ejection fraction was 48.9 ± 8.5%. Area at risk and infarct size indexed to LV mass were 30 ± 17% and 18 ± 12%, respectively. Infarct transmurality was 78 ± 25%. Microvascular obstruction was present in 85 patients (47%), intramyocardial hemorrhage in 33 patients (18%). Pericardial injury was depicted in 87 patients (48%), i.e., effusion (n = 30), enhancement (n = 46), mixed effusion/enhancement (n = 11) (Fig. 1). Patients showing pericardial injury presented higher CRP values ($p < 0.001$) than those with normal pericardial findings. They also showed higher troponin I values ($p < 0.001$). Other baseline characteristics, including time to PCI and TIMI grade flow grade (before and after reperfusion), were not significantly different from those without pericardial injury. A significant correlation was observed between CRP values and (a) LV ejection fraction and infarct size, (b) myocardial hemorrhage, microvascular obstruction and pericardial injury, and (c) cardiac biomarker values (Table 1). However, multivariate median (quantile) regression analysis showed that pericardial injury was the strongest and only independent predictor of CRP increase early post-infarction ($p = 0.006$) (Table 2). Pericardial damage showed an inconsistent effect across the spectrum of CRP. No significant effect was present at low CRP levels (1st quartile: $p = 0.100$), however the influence of pericardial damage increased progressively with higher CRP values (2nd and 3rd quartiles: $p = 0.015$) and the strongest influence was found at the highest CRP quartile ($p = 0.001$) (Fig. 2).

In agreement with recent studies, the current study findings confirm that the rise in inflammatory biomarkers is related to the severity of myocardial damage as evidenced by infarct size and transmurality and the presence of microvascular obstruction and/or intramyocardial hemorrhage [4,5]. However, our study moreover emphasizes a strong, if not the strongest, contribution of pericardial injury to the rise in CRP. Thus, as we previously reported, early post-infarction pericardial damage is not only closely related to the severity of myocardial damage, but the latter triggers a strong inflammatory pericardial response, which in itself substantially contributes to the rise in CRP [6]. The pericardial inflammatory component can explain the 15-fold increase in the magnitude of CRP, a phenomenon which is rather unlikely caused by the low intensity of interleukin-6 release from the injured myocardium. As CRP values rise above the median, regression analysis shows a strong relationship with pericardial damage, with almost 75% of patients showing of pericardial injury in the highest quartile (Fig. 2). Moreover,

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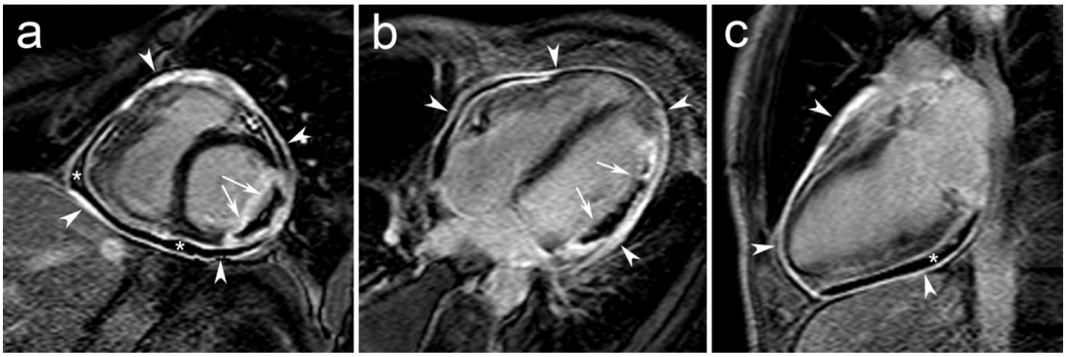

Fig. 1. Acute transmural lateral MI (arrows) with generalized extensive pericardial inflammation (arrowheads) and limited effusion (asterisk) in 39-year-old man presenting clinical signs of pericarditis (pain, pericardial rub) and a CRP value of 145 mg/dl. Note the presence of concomitant presence of no-reflow in the infarct area.

Table 1
Correlation between CRP and CMR, cardiac biomarkers and clinical related parameters.

Variables	Correlation	
	r	p-Value
CMR parameters		
LV ESV	0.20	0.006
LV EF	−0.28	<0.001
Infarct size (%of LV)	0.40	<0.001
Microvascular obstruction*	0.32	<0.001
Intramyocardial hemorrhage	0.44	<0.001
Size of area at risk	0.31	<0.001
Infarct transmurality	0.30	<0.001
Pericardial injury*	0.49	<0.001
Cardiac biomarkers		
Peak Tn I	0.34	<0.001
Peak CK-MB	0.32	<0.001
Others		
Anterior infarct location*	0.21	0.015
Time to PCI	0.22	0.007

CK-MB, creatine kinase MB fraction; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricle; MI, myocardial infarction; TnI, troponin I; time to PCI, time until reperfusion.
* Dichotomous variables were assessed with rank bi-serial correlation.

Table 2
Median (quantile) regression analysis for the prediction of peak CRP value at day 2.

Variables at baseline (1 week)	Coefficient (95% CI)	p-Value
Pericardial damage	23.137 (6.718 to 39.557)	0.006
Microvascular obstruction	7.437 (−11.563 to 26.438)	0.439
Intramyocardial hemorrhage	6.817 (−14.642 to 28.278)	0.530
Infarct size (% of LV)	0.958 (−11.563 to 0.985)	0.831
Size of area at risk	0.035 (−0.430 to 0.501)	0.880
Time to PCI	0.017 (−0.036 to 0.071)	0.515

the pattern of pericardial enhancement at late gadolinium enhancement CMR found in infarct patients is similar to the enhancement pattern found in patients with inflammatory pericarditis [7,8].

In conclusion, the rise in inflammatory biomarkers early post-infarction is to a large extent caused by pericardial injury, which in itself is an indirect marker of infarct severity. These findings underscore the intricate relation between infarct-related tissue damage and biomarkers.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

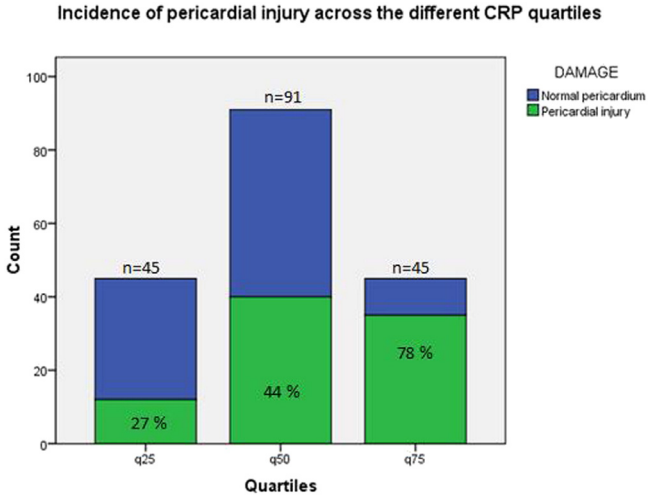

Fig. 2. Incidence of post-infarct pericardial injury. Gradual increase in the incidence of post-infarct pericardial injury across the different CRP quartiles (inc.q25 = 27%, inc.q50 = 44%, inc.q75 = 78%, $p < 0.001$). Between groups: $p < 0.001$ for q75, and $p = 0.0508$ between q25 and q75. q25; first CRP quartile (<9 mg/dl), q50; median CRP quartile (9–52 mg/dl), q75; third CRP quartile (>52 mg/dl), n; number of patients in each quartile.

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